REMARKS

Prior to entry of the amended claims presented above, claims 24-51 were pending in the application and stood rejected. In the present amendment, claim 24 has been amended to basically incorporate the features of cancelled claim 50, and therefore does not require a new search. Claims 31, 36, 38 41, 46, and 47-49 have been amended to correct the indefiniteness issues raised by the Examiner. Claim 50 has been canceled. Therefore, applicants respectfully request entry of this amendment, as it cancels a claim and places the claims in better condition for appeal.

Objection to the Specification

Applicants have already amended the specification to comply with the Examiner's requirement.

Rejections Under 35 USC §103(a)

Claims 24-51 are rejected under 35 USC § 103(a) as being unpatentable over WO 96/00237 taken with Josic et al. (J. Chromatogr. B. Biomed Appl., Vol. 662, No. 2, pp. 181-190, 1994), Grandgeorge et al (U.S. Patent No. 5,371,195) and Farb et al (U.S. Patent No. 4,758,657). Applicants respectfully traverse this rejection.

WO 96/00237

The Examiner states that "WO 96/00237 teaches a method of virus-filtering a solution that contains, *particularly factor VIII.*" (Office Action dated July 29, 2002, at page 4) (emphasis added). The Examiner states that support for this proposition is found at the abstract, page 5, lines 14 to 24, and claim 1. The Examiner also states that at page 7 line 30 to page 9, line 27, that WO 96/00237 teaches the use of "15 nm for the intended purpose of reducing the content of very small non-enveloped viruses, such as paroviruses, polio virus, hepatitis virus, etc." The Examiner then concludes that "the primary reference clearly teaches a method for obtaining a variety of safe solution of the plasma protein complex such as FVIII by a filtration step using a filter with a porosity of 15 nm." Applicants contend that when read in its entirety, WO 96/00237 does not in fact support this allegation and teaches away from the present invention.

When the whole of WO 96/00237 is examined, this reference does not support a teaching that a 15 nm filter can be used for factor VIII filtering, nor does this reference support a reasonable expectation of success. Specifically, WO 96/00237 discloses that the suitable filter for factor VIII is "VIRESOLVE™/180," which is suitable for "proteins having a molecular weight of up to about 180,000," which is an explicit teaching away from the present invention. Therefore, as a matter of law, because this reference does not (1) teach all of the elements of claim 24, (2) does not provide reasonable expectation of success in arriving at the present invention, or (3) suggest the present invention of claim 1, this reference cannot support a *prima facie* establishment of obviousness.

First of all, applicants note that the Examiner only uses WO 96/00237 in combination with other references to establish an obviousness rejection, thereby establishing that WO 96/00237 *per se*, does not teach all of the elements of claim 24. Applicants agree that WO 96/00237 *per se* does not teach all of the elements of claim 24 interpretation. Although (a) "factor VIII protein" and (b) a 15 nm filter are both mentioned in disparate sections of the 35-pages WO 96/00237, there is no nexus between this separate feature nor any explicit or implicit suggestion that these two features are combinable into a single process. Neither in the sections cited by the Examiner, nor in the other parts of this reference, is there a teaching that a factor VIII solution can be filtered with a 15 nm filter. Applicants will first discuss the sections cited by the Examiner.

The Abstract

The abstract mentions neither factor VIII nor a 15 nm filter. In fact, the only protein mentioned in the abstract is plasma protein factor *IX*, which was obtained in a "yield of 70% to above 90% by the "dead-end" filter technique. (Emphasis added). Besides protein factor IX, no other specific proteins are mentioned.

Pages 5-6

These pages mention factor VIII for the first and only time in the application. The description here is merely to state that "[p]referred types of factor VIII are deletion derivatives of recombinant produced factor VIII products." An advantage to the recombinant product is that it "lacks the inactive intermediate part of the natural factor VIII molecule." Accordingly, "[t]his gives the molecule a mean weight of about 170,000." An appropriate filter size is not given for factor VIII. Thus, factor VIII is described once generically and never as a working example.

Claim 1

Claim 1 provides no further guidance and merely reads "A method of virus-filtering a solution containing at least one macromolecule, characterized in that the total salt content of the solution lies within the range of from about 0.2M up to saturation of the solution with the salt concerned."

Pages 7-9: A teaching away

These pages, the most relevant paragraphs related to choice of filter size are reproduced below. Although the PLANOVA 15 is mentioned once, there is no elaboration on suitable macromolecules that can be filtered with a filter of this size. In fact when these paragraphs are read in their entirety, they teach away from the present invention. They explain the art known principle at the time, which is a filter has a degree of fineness, given in terms of "pore size or the approximate molecular weight (relative molecular mass) at which that molecules are stopped by the filter." Thus, as stated in these paragraphs, a filter membrane of a pore size of 70 would be suitable for molecules having up to a 70 kD molecular mass, while a 180 membrane filter would be suitable for a protein with a 180 kD molecular mass. Finally, as mentioned previously, these paragraphs only support the use of a 180 filter for factor VIII, because factor VIII is taught as having a molecular weight of around 170 kD. Therefore, when this reference is read in its entirety, one of skill in the art would only expect a filter of around 180, not 70, or much less 15 to be suitable for practicing the present invention.

> The degree of fineness of filters generally, is normally given as pore size or the approximate molecular weight (relative molecular mass) at which the molecules are stopped by the filter, the so called cut-off. In the present invention, the virus filters can have a cut-off of about 1,000,000, suitably 500,000. To remove small viruses, the virus filters should have a cut-off of 200,000, preferably 100,000. To reach a maximum virus-reduction, the virus filter should have a cut-off slightly higher than the macromolecule which is virus-filtered.
>
> Virus filters are known in the art and are supplied by Millipore from Massachusetts, USA and Asahi Chemical Industry Co., Ltd. From Japan, among others. Millipore supplies filters having two different types of membrane, depending on the size of the protein concerned. For instance, Millipore supplies, among others, VIRESOLVE™/70 for proteins having a molecular weight, or relative molecular mass, of up to about 70,000 and VIRESOLVE™/180 for proteins having a molecular weight of up to about 180,000. This latter filter can

be used for monoclonal antibodies, for instance. Asahi Chemical Industry supplies, among other things, Planova™35 and Planova™15 filters, this latter filter being used to remove smaller viruses, such as the polio virus.

As mentioned before, the choice of filter will depend on the size of the protein concerned, among other things. Factor IX, antithrombin III, human serum albumin (HAS) and Apo A-IM (the dimer) all have a molecular weight of roughly 60,000-70,000, wherein VIRESOLVE™/70, for instance, is a suitable alternative. Gammaglobulin has a molecular weight of about 180,000, wherein VIRESOLVE™/180, for instance, is a suitable alternative. The latter filter is also suitable for use with the recombinant produced factor VIII product, r-VIII SQ, which has a molecular weight of about 170,000, as mentioned before.

The Working Examples of WO 96/00237, as shown in the below table, were prepared in accordance with these teachings.

TABLE I

EXAMPLES	FILTER	PROTEIN	MASS OF PROTEIN (kD)
1-7; 14-16; 22	VIRESOLVE ™/70	Factor IX	60-70
8-11; 20	VIRESOLVE ™/180	Gammaglobilin	180
12-13; 19	VIRESOLVE ™/70	HSA	60-70
17-18; 21	VIRESOLVE ™/70	AT III	60-70

Other References

The teachings of the references, namely Josic et al. (J. Chromatogr. B. Biomed Appl., Vol. 662, No. 2, pp. 181-190, 1994), Grandgeorge et al (U.S. Patent No. 5,371,195) and Farb et al (U.S. Patent No. 4,758,657), do not further remedy the shortcomings of WO 96/00237. As acknowledged by the Examiner, none of these references teach a 15 nm filter for use with factor VIII. In fact, none of these references mention a 15 nm filter at all. Josic is related to using anion chromatography for purifying factor VIII and von Willebrand factors from human plasma and does not discuss subsequent filtering. Grandgeorge does not discuss a membrane filtration process. The only mention of filtering is in Example 1, where a DEAE-SEPHAROSE Fast Flow gel filter is used. Likewise, the only discussion of filtering in

Farb, at column 5, lines 47-53, is a very generic discussion of filtering and is reproduced below.

> The eluate so collected yields a solution having a Factor VIII:C potency of 10 to 50 Units per ml. The collected eluate can be sterile filtered per se and used as an infusable formulation for therapeutic purposes or can be further processed as a source of Factor VIII:C. Alternatively, the solution may be sterile filtered and lyophilized for storage prior to therapy.

In conclusion, no combination of WO 96/00237 taken with Josic et al. (J. Chromatogr. B. Biomed Appl.; Vol. 662, No. 2, pp. 181-190, 1994), Grandgeorge et al (U.S. Patent No. 5,371,195) and Farb et al (U.S. Patent No. 4,758,657), renders the present invention obvious, and therefore applicants request withdrawal of this rejection.

Manufacturer's Catalogs

Applicants submit in an IDS concurrent with this response a catalog, from the maker of PLANOVA filters with a publication date no later than 1997. This catalog shows that the maker of the PLANOVA filter did not produce any test results for using the PLANOVA 15 filter for factor VIII. This supports the argument that one of ordinary skill would not have been motivated to use the PLANOVA 15 filter for factor VIII filtering.

With respect to the manufacturer's catalog submitted in the response to the first Office Action, applicants wish to clarify that this catalog is not prior art, as this catalog was published after the filing date of the present application. Furthermore, applicants wish to restate the remarks they filed in the Response dated May 20, 2002 with respect to the manufacturer's catalog attached thereto. Upon a second review of the manufacturer's catalog, applicants note that the catalog discloses different results for "Factor VIII, >300 kD" and "Factor VIII (vWF dissociated) [at or around] 300 kD," with respect to the 15N PLANOVA filter. Apparently, this catalog discloses that the 15N PLANOVA filter is suitable for "Factor VIII (vWF dissociated) [at or around] 300 kD," but is not suitable for "Factor VIII, >300 kD."

Rejections Under 35 USC §112

With respect to all of the rejections for indefiniteness, applicants have amended the claims to render these rejections moot, except for the rejection to claims 48 and 49 with respect to the phrase "wherein the protein content." Applicants contend that one of ordinary skill in the art would understand that a factor VIII solution would contain protein. Moreover, the weight of protein in a factor VIII solution, *i.e.* the amount of milligrams per

milliliter, could easily be figured out. Therefore, the antecedent basis for this phrase is inherently present in claim 24, because claim 24 has an inherent protein weight. Accordingly, applicants contend that amendment of this phrase is not necessary to meet the statutory requirements for definite claim language.

CONCLUSION

In view of the above remarks and amendments, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

If any additional extension(s) of time are required for the filing of this paper, applicants expressly petition for such extension(s) and authorize the Commissioner to charge any deficiency to Deposit Account 19-0741.

Respectfully submitted,

January 22, 2003
Date

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

MARKED UP VERSION OF THE AMENDED CLAIM

24. **(Amended Once)** A method for preparing, a factor VIII solution that is [~~essentially~~]free of viruses and[~~essentially~~] devoid of vWF (von Willebrand factor) and factor VIII-vWF complexes, comprising:

(a) obtaining a starting factor VIII solution devoid of factor VIII-vWF complexes; and

(b) filtering said solution through a hydrophilic virus filter**, wherein the virus filter has a mean pore size of 15 ± 2 nm**..

31. **(Amended Once)** Method according to claim 28, wherein the Ca^{2+} ion is added in the form of a $CaCl_2$ solution[~~,~~] 0.35 M to saturation.

36. **(Amended Once)** A method according to claim 25, wherein the starting factor VIII solution [~~of (a)~~] **devoid of factor VIII-vWF complexes** is obtained by ion exchange chromatography.

38. **(Amended Once)** A method according to claim 36, wherein the starting factor VIII [~~fraction~~] **solution devoid of factor VIII-vWF complexes is** obtained **by ion exchange chromatography, and wherein** at the end of the [~~purification by~~]ion exchange chromatography**, the starting factor VIII solution devoid of factor VIII-vWF complexes** is eluted under the conditions of the disassociation of the factor VIII-vWF complexes.

41. **(Amended Once)** A method according to claim 24, wherein the starting factor VIII solution is treated with an effective amount of an anti-viral solvent [~~and/~~]or detergent**, or both**.

46. **(Amended Once)** A method according to claim 24, wherein the concentration[~~C~~] of the starting factor VIII solution is from approximately 2 to approximately 100 U/ml.

47. **(Amended Once)** A method according to claim 47, wherein the concentration [~~C~~]of the starting factor VIII solution is[~~from~~] approximately 10 to approximately 50 U/ml.

48. **(Amended Once)** A method according to 24, wherein the protein content of the starting factor VIII solution is[~~from~~] approximately 0.05 to approximately 0.5 mg/ml.

49. **(Amended Once)** A method according to 49, wherein the protein content of the starting factor VIII solution is[~~from~~] approximately from approximately 0.1 to approximately 0.5 mg/ml.